UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/589,255	06/07/00	LINK	P04091US1

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EXAMINER	
BECKERLEG,A	

ART UNIT	PAPER NUMBER
1632	4

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/589,255	LINK ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice To comply* .

DETAILED ACTION

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the rejections set forth below. Failure to comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-12, and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent No. 5,869,035, Feb. 9, 1999, hereafter referred to as the '035 patent. It is noted that although the 5,869,035 patent and the instant application are commonly assigned to the Human Gene Therapy Research Institute, the inventive entities of the two are different. The '035 patent lists Charles J. Link, Jr. and John P, Levy as inventors whereas the instant application lists Charles J. Link , Jr. and Tatiana Seregina. Therefore, in view of the different inventorship, the above claims are rejected over the '035 patent under both obviousness-type double patenting and 35 U.S.C. 102(e), see below.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The '035 claims recite broad methods of killing tumors comprising delivering to said tumor cells a vector producer cell line with a polynucleotide sequence that comprises a recombinant HSV plasmid vector that expresses $\alpha(1,3)$ galactosyltransferase. The '035 claims are broad and do not specifically recite the species of the vector producer cells or the species of the host. However, the '035 specification teaches that the preferred host is an old world monkey or human which does not express $\alpha(1,3)$ galactosyl epitopes and that the preferred vector producer cell line is a murine cell line (the '035 patent,

column 3, and column 7, lines 1-6). The '035 claims also do not specifically recite that hyperacute rejection causes tumor killing or that an innocent bystander immune response is generated. However, the '035 specification teaches that mechanism of tumor cell killing is hyperacute rejection mediated largely by complement activation ('035 specification, abstract, and column 4). Further, case law states that, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). Thus, as the structure of the xenogeneic cells taught by the '035 patent are identical to those claimed by the applicant, any and all properties of the xenogeneic producer cells are considered inherent. Therefore, while the '035 claims are broader than the instant claims, the '035 patent clearly teaches all the recited limitations of the instant claims and as such renders the instant claims obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of a solid tumor

comprising the direct administration to a solid tumor of a xenogeneic retroviral producer cell line which comprises a retrovirus encoding HSV-TK alone or in combination with α(1,3) galactosyltransferase, followed by the administration of gancyclovir, does not reasonably provide enablement for methods of treating tumors or methods of treating tumor comprising inducing hyperacute rejection wherein the method steps comprise the injection or infusion of any and all xenogeneic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses the treatment of tumors in humans comprising the administration of xenogeneic cells. In particular, the applicant discloses the administration of murine retroviral producer cells which naturally express α(1,3) galactosyl epitopes and which further produce a retrovirus which expresses HSV-TK. The applicant provides working examples of the instant invention which demonstrates that the intratumoral injection of murine retroviral producer cell lines encoding HSV-TK followed by ganciclovir in humans results in decreased tumor growth. The applicant also provides a working example demonstrating that human tumor cells transduced with a retrovirus encoding α(1,3) galactosyltransferase are susceptible to complement mediated lysis in the presence of human serum.

The specification does not provide an enabling disclosure for the induction of treatment of tumors by inducing hyperacute rejection through any means or by the injection/infusion of any type of xenogeneic cells to any type of host mammal. The specification is directed to the

generation of hyperacute immune responses in humans against α(1,3) galactosyl epitopes that are present on non-old world primates, such as humans. The specification does not disclose any other protein, glycoprotein or carbohydrate which causes hyperacute rejection of cells expressing the protein, glycoprotein or carbohydrate in vivo in humans or in any other mammals. Further, as α(1,3) galactosyl epitopes are expressed in the majority of mammals, the disclosed methods of inducing hyperacute immune responses to α(1,3) galactosyl are therefore limited to the introduction of non-old world primate cells to old world primates such as humans. It is also noted that the specification fails to disclose any means for inducing hyperacute rejection other than the introduction of murine vector producer cell lines which express a retrovirus encoding a gene such as HSV-TK or α(1,3) galactosyltransferase to humans. In addition, the specification, while demonstrating that murine retroviral producer cells expressing HSV-TK are killed by hyperacute rejection in vivo in patients and that humans cells transduced with α(1,3) galactosyltransferase are lysed by human serum in vitro, fails to provide sufficient guidance as to the level of expression of α(1,3) galactosyl epitopes or the level of complement activation required to induce hyperacute immune responses in vivo and further to produce a therapeutic immune or innocent bystander effect on local tumor cells. Although the specification and the art at the time of filing disclose that the introduction of xenogeneic cells such as murine or porcine cells to humans results in their rapid destruction by complement fixation or preformed anti-xenogeneic antibodies, neither the art nor the specification provides any evidence that the destruction of the any xenogeneic cell or xenogeneic viral producer cell in vivo results in any observed tumor treatment in the absence of

tk/ganciclovir therapy. Thus, from the teachings in the art and the data provided in applicant's specification, it would appear that hyperacute immune responses to a xenogeneic cell alone are not sufficient to induce significant killing of tumor cells.

It is also noted that the specification fails to provide guidance for the expression of any genes other than HSV-TK and α(1,3) galactosyltransferase in the xenogeneic cells of the instant invention or teach that the expression of any other gene in a xenogeneic cell results in immune mediated bystander killing of tumors. At the time of filing, the art taught that the immunotherapy of tumors using cell based and/or gene based therapies was considered highly unpredictable. Ross et al. relates that while, " there is only 1 patient to date who might be considered to have had a significant systemic clinical response " to cytokine therapy of a melanoma, "success in a single patient does not imply the general utility of this approach" (Ross et al. (1996) Human Gene Therapy, Vol. 7, page 1786, column 1, paragraph 4). Orkin et al. concurs, stating in regards to the immunotherapy of cancer that, " although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans", and that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) page 1, paragraph 3, page 6, paragraph 6). In regards to the use of currently available vector systems for the expression of therapeutic genes, Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Verma et al.

also teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy of disease. The specification does not provide any guidance as to vectors other than retroviral vectors useful for delivering HSV-TK and/or α(1,3) galactosyltransferase to tumor cells in vivo such that a therapeutic response of the tumor is induced. It is further noted that the specification fails to provide any guidance in the form of specific teachings or working examples that the induction of hyperacute immune responses in the vicinity of a tumor is capable of reversing chemotherapeutic resistance in a tumor. Thus, in view of the art recognized unpredictability of inducing therapeutically effective anti-tumor immune responses in vivo, the lack of guidance provided by the specification for means of inducing a hyperacute response in any mammal other than the administration of viral producer cells which express HSV-TK or α(1,3) galactosyltransferase, the lack of guidance concerning xenogeneic cell selection and/or vector/gene selection such that the level of induced hyperacute immune responses in vivo correlates with tumor killing, the limitation of the working examples to the administration of murine vector producer cells which produce a retrovirus encoding HSV-TK and/or α(1,3) galactosyltransferase, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed and the skilled artisan would not have predicted success in treating tumors by inducing hyperacute immune responses using any means in the vicinity of the tumor.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8, and 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The recited method does not recite any particular method steps. The method recites a method of treating tumors comprising inducing hyperacute rejection in and/or in the vicinity of the tumor. However, the method fails to recite any particular step which results in the induction of hyperacute rejection. In the absence of any particular recited method steps, these claims are indefinite as it is unclear what exactly are the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4, 6-12, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,869,035, Feb. 9, 1999, hereafter referred to as the '035 patent. It is noted that

although the 5,869,035 patent and the instant application are commonly assigned to the Human Gene Therapy Research Institute, the inventive entities of the two are different. The '035 patent lists Charles J. Link, Jr. and John P, Levy as inventors whereas the instant application lists Charles J. Link , Jr. and Tatiana Seregina. Therefore, in view of the different inventorship, the above claims are rejected over the '035 patent under both obviousness-type double patenting and 35 U.S.C. 102(e), see above.

The applicant claims methods of treating tumors comprising adding xenogeneic cells to the peritoneal space around or within a tumor which activates hyperacute rejection to the cells and an immune reaction to the tumor and methods of treating tumors comprising inducing hyperacute rejection in and/or in the vicinity of the tumor. The applicant further claims said methods wherein the subject is human and the xenogeneic cells are murine vector producer cells which express α(1,3) galactosyl epitopes.

The '035 patent teaches methods of killing tumors comprising delivering to said tumor cells a vector producer cell line with a polynucleotide sequence that comprises a recombinant HSV plasmid vector that expresses α(1,3) galactosyltransferase ('035 patent, claims 4-7). The '035 specification further teaches that the preferred host is an old world monkey or human which does not express α(1,3) galactosyl epitopes and that the preferred vector producer cell line is a murine cell line (the '035 patent, column 3, and column 7, lines 1-6). The '035 specification also teaches that the mechanism of tumor cell killing is by hyperacute rejection mediated largely by complement activation ('035 specification, abstract, and column 4). It is noted that case law states

that, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). Thus, as the structure of the xenogeneic cells taught by the '035 patent are identical to those claimed by the applicant, any and all properties of the xenogeneic producer cells are considered inherent. Therefore, by teaching all the limitations of the claims, the '035 patent clearly anticipates the instant invention.

Claims 1, 3-4, 6, 9-12, and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,045,789, 4/4/00 (EFD 5/1/92), hereafter referred to as Culver et al. The applicant claims methods of treating tumors in a subject comprising adding an amount of xenogeneic cells to the peritoneal space around or within the tumor which activates hyperacute rejection of the cells and an immune reaction to the tumor, and methods of treating tumors comprising inducing hyperacute rejection in and/or in the vicinity of the tumor. The applicant further claims said methods wherein hyperacute rejection comprises infusion or xenotransplantation of xenogeneic cells which have a surface glycosylation pattern that includes $\alpha(1,3)$ galactosyl epitopes, and wherein said tumors are solid tumors selected from a group which includes ovarian carcinomas.

Culver et al. teaches the injection of a murine retroviral packaging cell line which produces a retrovirus encoding HSV-TK to a solid tumor in a subject resulting in tumor treatment following ganciclovir administration (Culver et al., column 13, lines 39-57, and column 14, lines

1-14, and claims 1-5). Culver et al. teaches that the intended subject for the disclosed method is a human cancer patient (Culver et al., columns 1-2). Culver et al. further teaches that the administration of the murine HSV-TK retrovirus producing cell to the tumor resulting in bystander killing of tumor cells which do not express HSV-TK (Culver et al., see for instance columns 4). While Culver does not explicitly teach that the murine cells express α(1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α(1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α(1,3) galactosyl epitopes. In addition to the expression of HSV-TK, Culver et al. also teaches that the retrovirus may encode immune response-enhancing genes which activate a particular constituent of the immune system or which stimulates the proliferation of cells associated with an immune response (Culver et al., columns 8-9, lines 39-67 and 1-26). For example, Culver teaches the inclusion of IL-2 in the retrovirus, a cytokine which has been previously demonstrated to have generate therapeutic anti-tumor immune responses in humans (Culver et al., column 9, lines 4-12). In addition, Culver teaches that the disclosed method is useful for treating a number of solid tumors including ovarian tumors (Culver et al., column 10, 13-21). Thus, Culver teaches the treatment of tumors comprising the administration of xenogeneic murine retrovirus producing cells directly to a tumor in a subject which includes humans wherein the murine cells produce a retrovirus which encodes HSV-TK and IL-2 such that an immune response is generated against the tumor and that tumor cells are also killed directly by HSV-TK/ganciclovir or indirectly by innocent bystander effect. By teaching all the limitations of the claims, Culver et al. anticipates the instant invention as claimed.

Claims 1-4, 6-12, and 15 are rejected under 35 U.S.C. 102(a) over Klatzmann et al. (1998) Human Gene Therapy, Vol. 9, 2585-2594. The applicant claims methods of treating tumors in a subject comprising adding an amount of xenogeneic cells to the peritoneal space around or within the tumor which activates hyperacute rejection of the cells and an immune reaction to the tumor, and methods of treating tumors comprising inducing hyperacute rejection in and/or in the vicinity of the tumor. The applicant further claims said methods wherein hyperacute rejection comprises infusion or xenotransplantation of xenogeneic cells which have a surface glycosylation pattern that includes α(1,3) galactosyl epitopes, and wherein the immune reaction is an innocent bystander effect.

Klatzmann et al. teaches the treatment of melanoma tumors in humans by direct intratumoral injection of a xenogeneic murine retroviral producing cell line that produces a retrovirus encoding HSV-TK followed by the administration of ganciclovir (Klatzmann et al., page 2585). While Klatzmann et al. does not explicitly teach that the murine retroviral producer cells express α(1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α(1,3) galactosyltransferase in protein glycosylation and that murine proteins contain α(1,3) galactosyl epitopes. Klatzmann et al. observed local inflammatory reactions at the tumor site following the injection of the xenogeneic cells and specifically states that the transplanted murine cells are rejected within 7-10 days as a result of hyperacute rejection mediated by preformed antixenogeneic antibodies and complement (Klatzmann et al., page 2585, abstract). Klatzmann et al., while teaching the exact steps recited in the instant claims, does not explicitly teach that the

administration of the xenogeneic retroviral producer cells generates an immune response against the tumor cells themselves or that the immune response causes an innocent bystander response resulting from the hyperacute rejection of the xenogeneic cells. However, Klatzmann et al. did observe tumor necrosis as a result of this therapy. It is further noted that the specification's own analysis of these results and other *in vivo* HSV-TK clinical trials in humans states that these results suggest that innocent bystander killing of tumor cells has occurred as result of the hyperacute rejection of the xenogeneic murine retroviral producer cells. Thus, it would appear that the ability of xenogeneic murine retroviral producer cells which produce a retrovirus encoding HSV-TK to generate hyperacute immune responses in a human which result in innocent bystander killing of tumor cells is an inherent property of the xenogeneic murine retroviral producer cells . Further, case law states that, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). Thus, by teaching all the limitations of the instant methods, Klatzmann et al. anticipates the invention as claimed.

The applicant is also reminded that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught

by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, and 9-17 are rejected under 35 U.S.C. 103 over U.S. Patent No. 6,045,789, 4/4/00 (EFD 5/1/92), hereafter referred to as Culver et al. in view of Link et al. (1998) Human Gene Ther., Vol. 9(1), 115-134, and further in view of Link et al. (1998) Anticancer Res., Vol. 18, 2301-2308, here after referred to as Levy et al.. It is noted that Levy et al. (1998) represents a

different inventive entity from that of the instant application as the authors of Link et al. and the inventors of the instant application as not identical. The applicant claims methods of treating tumors in a subject comprising adding an amount of xenogeneic cells to the peritoneal space around or within the tumor which activates hyperacute rejection of the cells and an immune reaction to the tumor, and methods of treating tumors comprising inducing hyperacute rejection in and/or in the vicinity of the tumor. The applicant further claims said methods wherein hyperacute rejection comprises infusion or xenotransplantation of xenogeneic cells which have a surface glycosylation pattern that includes α(1,3) galactosyl epitopes, and wherein said tumors are solid tumors selected from a group which includes ovarian carcinomas. In addition, the applicant claims said methods wherein the xenogeneic cells are murine retroviral producer cells which produce the LTKOSN.1 vector and which transduce the tumor cells with α(1,3) galactosyltransferase.

Culver et al. teaches the injection of a murine retroviral packaging cell line which produces a retrovirus encoding HSV-TK to a solid tumor in a subject resulting in tumor treatment following ganciclovir administration (Culver et al., column 13, lines 39-57, and column 14, lines 1-14, and claims 1-5). Culver et al. teaches that the intended subject for the disclosed method is a human cancer patient (Culver et al., columns 1-2). Culver et al. further teaches that the administration of the murine HSV-TK retrovirus producing cell to the tumor resulting in bystander killing of tumor cells which do not express HSV-TK (Culver et al., see for instance columns 4). While Culver does not explicitly teach that the murine cells express α(1,3) galactosyl epitopes, it is an inherent property of murine cells that they utilize α(1,3) galactosyltransferase in

protein glycosylation and that murine proteins contain α(1,3) galactosyl epitopes. In addition to the expression of HSV-TK, Culver et al. also teaches that the retrovirus may encode immune response-enhancing genes which activate a particular constituent of the immune system or which stimulates the proliferation of cells associated with an immune response (Culver et al., columns 8-9, lines 39-67 and 1-26). For example, Culver teaches the inclusion of IL-2 in the retrovirus, a cytokine which has been previously demonstrated to have generate therapeutic anti-tumor immune responses in humans (Culver et al., column 9, lines 4-12). In addition, Culver teaches that the disclosed method is useful for treating a number of solid tumors including ovarian tumors (Culver et al., column 10, 13-21). Thus, Culver teaches the treatment of tumors comprising the administration of xenogeneic murine retrovirus producing cells directly to a tumor in a subject which includes humans wherein the murine cells produce a retrovirus which encodes HSV-TK and IL-2 such that an immune response is generated against the tumor and that tumor cells are also killed directly by HSV-TK/ganciclovir or indirectly by innocent bystander effect.

Culver et al. differs from the instant invention by failing to teach the LTKOSN.1 vector. Culver et al. however does teach that many different types of retroviral vectors including replication-competent, replication-defective, amphotropic or xenotropic retroviral vectors are suitable for use in the disclosed methods. Link et al. supplements Culver et al. by teaching the LTKOSN.1 vector which can be produced by a murine retroviral producer cell line and which can be used for the killing of cells in combination with ganciclovir (Link et al., abstract). Thus, based on the teachings of Culver et al., that many different retroviral vectors encoding HSV-TK can be

used to treat tumors using the disclosed methodology, and the successful expression of HSV-TK in cells using the LTKOSN.1 vector taught by Link et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the LTKOSN.1 vector taught by Link in the method of treating tumors taught by Culver et al., and the skilled artisan would have had a reasonable expectation of success in transducing tumor cells with the LTKOSN.1 vector.

Neither Culver et al. nor Link et al. teaches the addition of the gene for α(1,3) galactosyltransferase to a retrovirus encoding HSV-TK. Culver, however, as discussed above, does teach the addition of genes which encode immune response-enhancing genes which activate a particular constituent of the immune system or which stimulates the proliferation of cells associated with an immune response (Culver et al., columns 8-9, lines 39-67 and 1-26). Levy et al. supplements Culver et al. and Link et al. by teaching methods of inducing hyperacute rejection of human tumor cells by contacting the tumor cells with murine retroviral producer cells which express α(1,3) galactosyltransferase (Levy et al., pages 2301-2302). Thus, in view of the motivation to include genes which encode immune response-enhancing genes which activate a particular constituent of the immune system in a retroviral vector encoding HSV-TK provided by Culver et al., and further in view of the successful generation of hyperacute immune responses against tumors exposed to retroviral producer cells expressing α(1,3) galactosyltransferase, it would have been *prima facie* obvious to the skilled artisan to modify the HSV-TK retroviral vectors taught by Culver et al. or Link et al. to further include the α(1,3) galactosyltransferase as taught by Levy et al. in order to generate hyperacute rejection of tumors and overall tumor

treatment. Further, based on the successful killing of human tumor cells using both retrovirus encoded HSV-TK or α(1,3) galactosyltransferase, the skilled artisan would have had a reasonable expectation of success in treating tumors by combining the two therapeutic modalities in a single retroviral producer cell.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The art unit fax number is (703) 308-8724.

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